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1: Eur J Neurosci 2001 Mar;13(5):899-908

P2Y receptor-mediated inhibition of voltage-activated Ca(2+) currents in PC12 cells.

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To search for inhibitory nucleotide receptors in the sympathoadrenal cell lineage of the rat, voltage-activated Ca(2+) currents were recorded in PC12 cells after differentiation with nerve growth factor. ADP and ATP, but not uridine nucleotides, reduced Ca(2+) current amplitudes and slowed activation kinetics. This effect was mediated by GTP binding proteins, as it was abolished by intracellular GDP beta S and after treatment with pertussis toxin. Furthermore, depolarizations preceding the activation of Ca(2+) currents abolished the ADP-induced slowing of activation kinetics and attenuated its inhibitory action on current amplitudes. The modulatory effect of ADP was neither altered in the presence of adenosine receptor antagonists, nor mimicked by agonists at these receptors. In addition, the action of ADP was antagonized by reactive blue 2, but not by suramin or PPADS. Nucleotides tested for their inhibitory action on Ca(2+) currents displayed the following rank order of potency: 2-methylthio-ADP > or = 2-methylthio-ATP >> ADP beta S > ADP = ATP. When P2X receptors were blocked, the P2X agonists ATP and 2-methylthio-ATP still reduced Ca(2+) currents. The P2Y1 receptor antagonists adenosine-2'-phosphate-5'-phosphate and adenosine-3'-phosphate-5'-phosphate did not alter the inhibitory action of ADP, whereas the Sp-isomer of adenosine-5'-O-(1-thiotriphosphate) and 2'- and 3'-O-(4-benzoylbenzoyl)-ATP showed significant antagonistic activity. These results demonstrate that PC12 cells express an as yet unidentified P2Y receptor with pharmacological characteristics similar to those of P2Y1. As receptor-dependent modulation of Ca(2+) channels is a key event in presynaptic inhibition, this receptor may correspond to previously described presynaptic nucleotide receptors mediating autoinhibition of sympathetic transmitter release.

PMID: 11264662 [PubMed - indexed for MEDLINE]